EASTMAN

Eastman Chemical Company
P.O. Box 511
Kingsport, Tennessee 37662

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2002 MAY -9 AM 11: 25

AR201-13736

May 1, 2002

Ms. Christine Todd Whitman, Administrator
US EPA
PO Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

RE: HPV Chemical Challenge Program, AR-201

Dear Ms Whitman:

On behalf of Eastman Chemical Company, I am pleased to submit the test plan and robust summaries for ethylene glycol diacetate (CAS No.: 111-55-7). My company had agreed to sponsor this chemical and provide the Agency with the enclosed information in the year 2003. However, due to the substantial amount of data that had been previously generated to understand the potential hazards of this chemical, we were able to complete our summarization ahead of schedule.

Enclosed with this letter is a computer diskette containing the test plan and robust summaries in Adobe Acrobat (.pdf) format. The HPV registration number for Eastman Chemical is

We understand this information will be posted on the internet for comments for a period of 120 days. Please forward comments to me at the above address.

Sincerely,

James A. Deyo D.V.M., Ph.D., D.A.B.T.
Technical Associate

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AR201-13736A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
ETHYLENE GLYCOL DTACETATE
(CAS NO.: 1 I l-55-7)

PREPARED BY:

EASTMAN CHEMICAL COMPANY

May 1, 2002

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OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for ethylene glycol diacetate (EGD; CAS NO.: 1 1 I-55-7) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use both the existing data on EGD in conjunction with data from ethylene glycol (a structural surrogate) and EPA-acceptable predictive computer models to adequately fulfill all the Screening Information Data Set (SIDS) endpoints. We believe that in total these data arc adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests. Furthermore, they follow the principles contained in the letter the EPA sent to all HPV Challenge Program participants on October 14, 1999 in which participants are directed to maximize the use of existing data for scientifically appropriate related chemicals in order to minimize animal testing.

Ethylene glycol diacetate is colorless low odor, very slow-evaporating liquid that is manufactured to a high degree of purity. This chemical finds its major use in thermoplastic acrylic coatings as a re-flow solvent and as an industrial intermediate as a slow release acetic acid source in silicate foundry core-binding applications. It is also used as a solvent in some printing inks. At this time the ACGIH has not established any industrial work place exposure levels for this chemical.

JUSTIFICATION FOR USE OF SURROGATE DATA

As a means to reduce the number of tests that may be conducted, the EPA allows for the use of categories or surrogate chemicals to group together chemicals that are structurally similar to characterize specific SIDS endpoints (USEPA 1999a). Accordingly, for the completion of some endpoints for ethylene glycol diacetate (EGD) this test plan utilizes data from ethylene glycol (EG) as a surrogate chemical. The toxicity of EGD to mammalian species is strongly believed to be a result of its metabolic conversion to EG by cleavage of the ester bonds. Chemicals held together through ester bonds are often readily split into the parent alcohol and acid moieties in biological systems through the action of various esterasc enzymes that arc located through out the body including the mucosal surfaces of the respiratory tract.

While anecdotal in nature? the clinical symptoms detailed in the Hazardous Substances Data Base (HSDB) following a toxicosis in humans with EGD is consistent with what occurs after a toxic exposure to EG. These include "I. Central nervous depression characterized by transient exhilaration, drunkenness, ataxia, and vertigo, progressing to stupor and finally coma, with or without a transient period of convulsions. 2. Death from respiratory arrest or perhaps cardiovascular collapse. 3. Nausea, vomiting, abdominal pain, dehydration, weakness, muscle tenderness. 4. Hyperpnea may indicate either metabolic acidosis or pulmonary edema. 5. Carpopedal spasm or other signs of hypocalcemic tetany. 6. Lumbar pain, albuminuria, hematuria, oliguria progressing to anuria. 7. Acute renal failure with uremia, peripheral edema, ascites, pulmonary edema, drowsiness, cyanosis, coma, and death in 7 to IO days, This observation lends further support to the hypothesis that EGD is metabolized to EG in humans and is most likely the etiological basis of its toxicity.

At this time, although there are no pharmacokinetic data detailing the actual rates at which EGD metabolizes into EG, there are such data available on several other types of similar compounds formed by ester linkages. These data demonstrate that the ester bond between an acetic acid and an alcohol is readily and rapidly cleaved and that the primary driver for systemic toxicity is the parent alcohol/glycol (the formation of the acetate ion often leads to irritation in nasal epithelial tissues under conditions of respiratory exposure). Examples of such molecules include methyl acetate, ethyl acetate and butyl acetate whose toxicity following exposure is well recognized to be due to the metabolic formation of the respective alcohol. Similarly, with glycol-ether acetate molecules the basis for toxicity is the glycol-ether parent. Examples of this include, the reproductive toxicity seen following exposure to ethylene glycol methyl ether (EGME) and ethylene glycol ethyl ether (EGEE) is also manifested following an exposure to their acctylated moieties (EGME-acetate and EGEE-acetate). Studies found in the literature have also demonstrated the formation of oxalic acid formation (a known EG metabolite) following exposure to PG-monoacetate. Since EGD is structurally similar to these aforementioned molecules, it is scientifically plausible to assume EGD will also be metabolized to EC.

Probably the most definitive of all the evidence supporting the supposition that EGD is cleaved into EG, which dictates its toxicity, is found in the results of repeat exposure studies conducted on EGD (see robust summary section). In one of the studies, it is reported that the kidneys of a rat that died after one week of exposure to EGD were filled with calcium oxalate crystals. The histological appearance of the kidneys were indistinguishable from test animals that had received EG alone in the same study. In a second EGD exposure study, it was noted that 4 of] 1 animals that died between Days 7 and 114, and 4 of the remaining 7 animals all had renal lesions that were associated with the presence of calcium oxalate crystals. These kidney lesions were also histologically similar to renal lesion from an exposure to EG. The identification of oxalate crystals in the urine of animals is almost pathognomic for an EG toxicosis. The acute oral toxicity in rats of EGD is also in the same range as EG (6.86 g/kg verse 4 – IO.2 g/kg, respectively).

In conclusion, even though much of the evidence for the metabolic conversion of EGD to EG is somewhat circumstantial in nature, it is still believed to be of sufficient strength to support a conclusion that data from EG can be used for some mammalian toxicity endpoints in lieu of information on EGD. Specifically, the data from EG is needed to assess the potential for EGD to induce reproductive and developmental toxicity. Furthermore, while data from repeat dose studies are available on EGD, its robustness and quality are limited (data are from old studies). Accordingly, in making a hazard assessment of EGD for this endpoint, one should also review information publicly available on EG.

TEST PLAN SUMMARY

CAS No. I I I-55-7	Information	OECD Study	O:her	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	Y	-	N	Y	N
Partition Coefficient	Y	-	Y	-	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	Y	-	-	Y	Y	N
Biodegradation	Y	Y	-	-	N	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	-	Y	-	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	-	Y	-	N	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	-	Y	-	N	Y	N
Repeated Dose Toxicity[1]	Y	-	Y	-	N	Y	N
Genetic Toxicity – Mutation	Y	-	Y	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity[1]	Y	-	-	-	-	-	N
Toxicity to Reproduction[1]	Y	-	-	-	-	-	N

1 This endpoint is either completed or supported through the use of data on ethylene glycol used as a surrogate.

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point -	A value for this endpoint was obtained from reputable textbook referenced within the Hazardous Substance Data Base (HSDB).
Boiling Point -	A value for this endpoint was obtained from reputable textbook referenced within the HSDB.
Vapor Pressure -	A value for this endpoint was obtained from reputable textbook referenced within the HSDB.
Partition Coefficient	A value for this endpoint was obtained from reputable textbook referenced within the HSDB.
Water Solubility -	A value for this endpoint was obtained from reputable textbook referenced within the HSDB.
Conclusion:	All end points haven been satisfied by the utilization of data obtained from reference values located in reputable textbooks identified by the HSDB. No new testing is required.

B. Environmental Fate

Photodegradation -	A value for this endpoint was obtained using AOPWIN, a computer estimation modeling program (1).
Stability in Water	This endpoint was filled by data from an abiotic degradation study that followed established guidelines and GLP assurances (OECD TG-111).
Biodegradation -	This endpoint was satisfied through data found within a peer-reviewed publication referenced in the HSDB. It is stated that OECD methods were used.
Fugacity	A value for this endpoint was obtained using the EQC Level III partitioning compute] estimation model within EPIWIN.
Conclusion:	All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models (2). In total, they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish -	This endpoint is filled by data from an OECD TG-203 study conducted under GLP assurances.
Acute Toxicity to Aquatic Invertebrates -	This endpoint is filled by data from an OECD TG-202 study conducted under GLP assurances.
Toxicity to Aquatic Plants -	This endpoint is filled by data from an OECD TG-201 study conducted under GLP assurances.
Conclusion:	All endpoints have been satisfied with data from well-conducted studies using OECD guideline methods and GLP assurances. They are all of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity - This endpoint is filled by oral exposure data found in a peer-reviewed journal. The study was completed quite some time ago and did not follow an established protocol. The quality of this study was still deemed as "reliable with restrictions" and little would be accomplished by conducting a new study. (The value referenced is similar to that of EG which is used as a surrogate for some endpoints.)

Repeat Dose Toxicity - This endpoint is filled by data from 2 oral exposure studies (drinking water) identified in peer-reviewed journals. Both had exposure durations of about 130 days. Neither study followed established protocols and both were completed quite some time ago. The quality of these studies was deemed as "reliable with restrictions" as they lacked much detail. However, their main functionality lies in the fact that the observations noted in these studies arc consistent with the assumption that the toxicity of EGD is due to its biological transformation to EG. Again data from EG alone should bc used when assessing the repeat dose hazard potential of EGD.

Genetic Toxicity

Mutation - This endpoint is filled with a study that followed established guidelines (EEC Annex V Guideline number B. 14) and GLP assurances. This study utilized *Salmonella typhimurium* (strains TA 98, 100, 1535, 1537, and 1538) and *Escherichia coli* (strain WP2*uvr*A). The quality of this study was deemed as "reliable without restrictions",

Aberration - This endpoint is filled with data from an *in vitro* study using Chinese hamster ovary (CHO) cells that followed OECD guideline #473 and was conducted under GLP assurances. The quality of this study was deemed as "reliable without restrictions".

Developmental Toxicity - This endpoint is tilled by data from ethylene glycol, which serves as surrogate chemical. A justification for its use has been provided. Robust summaries on EG for this end point can be found in the Ethylene Glycols category of chemicals being assessed under the International Council of Chemical Associations (ICCA) High Production Volume (HPV) Initiative.

Reproductive Toxicity - This endpoint is filled by data from ethylene glycol, which serves as surrogate chemical. A justification for its use has been provided. Robust summaries on EG for this end point can be found in the Ethylene Glycols category of chemicals being assessed under the International Council of Chemical Associations (TCCA) High Production Volume (HPV) Initiative.

Conclusion: All endpoints have been satisfied with data from studies whose methods followed established OECD guidelines, or utilized methods that were very similar and scientifically appropriate. The endpoints assessing reproductive and developmental toxicity utilize information available on EG, the presumed metabolite of EGD. Although actual data on EGD are available for assessing systemic toxicity from repeated exposures, it is recommended that data from EG be used as a supplement in evaluating the hazard potential of EGD for this endpoint. In total the data available on EGD or its surrogate (EG) are of sufficient quality to conclude that no additional testing should be performed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for EGD were all obtained from texts references found in the HSDB. These data indicate that EGD is a liquid at room temperature with a relatively low vapor pressure. It has a low estimated octanol to water partition coefficient and accordingly is quite soluble in water.

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of actual data and acceptable estimation modeling programs. As a result of its solubility in water and relatively low volatility, fugacity estimations predict that EGD will distribute primarily to soil and water. Results of an OECD TG 1 I 1 study demonstrate EGD will readily hydrolyze under basic conditions with a half-life of <2.5 hours. Results of a published biodegradation study classified EGD as readily degraded in the environment. It primary use is in coatings applications will results in environmental releases that occur primarily through evaporative emissions. EGD is expected to degrade in the atmosphere at a relatively fast to moderate rate with an estimated atmospheric half-life of <3 days.

The potential toxicity of EGD to fish, Daphnia, and algae were determined through well-conducted guideline studies. The results of these studies demonstrated that Daphnia and algae were not sensitive species with both having a NOEC >100 mg/L. However, the LC_{50} determination in fish was only 40.45 mg/L. Based on these data EGD would be classified as "harmful to aquatic organisms" according to the European Union's labeling directive but would be classified in a "moderate concern level" according to the U.S. EPA's assessment criteria. The potential for significant exposures to aqueous environments is unlikely accept under accidental conditions and it is noted as being readily biodegradable by waste water organisms. Interestingly, the LC_{50} determinations to ethylene glycol in the same species of fish were 53,000; 49,000; and 57,000 mg/L for fry, juvenile, and subadult fish, respectively. The basis of the wide gulf between these values and those observed for EGD is unknown.

The potential to induce toxicity in mammalian species following acute oral exposure is low with an LD_{50} value in rats of 6.86 g/kg. These data are analogous to those obtained on the parent molecule EG (5.89 - 13.4 g/kg). Data from two repeat exposure studies in rats in which EGD was put into drinking water at levels of 1 5% for **about** 130 days showed evidence of renal toxicity and formation of calcium-oxalate crystals. This finding is analogous to what may be seen following an exposure EC alone. Results from mutagenicity and chromosomal aberration studies indicate this material is not genotoxic. Developmental and reproductive toxicity endpoints were **assessed** through the use of a surrogate chemical ethylene glycol. Numerous studies can be found in the public literature for EG on these latter two endpoints, as well as others. Robust summaries will be available on ethylene **glycol** under the International Council of Chemical Associations (ICCA) High Production Volume (HPV) Initiative. The reproductive toxicity of EG is also undergoing a review by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (CERHR). The results of this review will also be available to the public.

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on EGD that either followed established protocols under GLP assurances or scientifically acceptable procedures to assess the various endpoints. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA, as well as through the use of surrogate data. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to workers and the general population as well as the environment.

EVALUATION OF DATA FOR OUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch *et al.* (4). These methods include consideration of the reliability, rclcvancc and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (5). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

I. Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or **in** which the test parameters are documented and comparable to these guidelines.

2. Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

3. Not Reliable: Includes studies or **data** in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

4. Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 3.01, Syracuse Research Corporation, Syracuse, New York.

2. US EPA. (1999). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

3 USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated I 1/2/98.

4. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol. 25: l-5.*

5 USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 211 0/99.

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I. General Information

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CAS Number: I I I-55-7
Name: I,2-Diacetoxyethane
I ,2-Ethanediol, Diacetate
Ethylene Acetate
Ethylene Diacetate
Ethylene Diethanoate
Ethylene Glycol Acetate
Ethylene Glycol Diacetate
Ethanediol Diacetate
Glycol Diacetate

II. Physical-Chemical Data

A. *Melting Point*

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity unknown
Method	
Method:	Not Specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Melting point value:	-3 1 °C
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 430
References	Budavari, S. (Ed.), The Merck Index -Encyclopedia of Chemicals, Drugs and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc 1989, 599.
Other	Last revision date: 19980602

B. Boiling Point

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Boiling point value:	190-191 ^{o}C
Pressure:	Not specified
Pressure unit:	
Decomposition:	
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 430
References	Budavari, S. (Ed.). The Merck Index – Encyclopedia of Chemicals, Drugs and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc 1989, 599.
Other	Last revision date: 19980602

C. Vapor Pressure

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Vapor pressure value:	0.077 mmHg
Temperature:	25 ^{o}C
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 430
References	Daubert, T.E. and Danner, R.P. Physical and Thermodynamic Properties of Pure Chemicals Data Compilation; Washington, D.C.: Taylor & Francis, 1989.
Other	Last revision date: 19980602

D. Partition Coefficient

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Log P_{ow}:	0.10-0.38
Temperature:	Unknown
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 430
References	Verschueren, K. Handbook of Environmental Data of Organic Chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold Co., 1983. 696
Other	Last revision date: 19980602

E. Water Solubility

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Value:	1.78X10+5 mg/l
Temperature:	24.5 ^{o}C
Description:	Appreciable (> 100 g/L)
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 430
References	Yalkosky, S.H., Dannenfelser, R.M.; The AQUALSOL dATAbASE of Aqueous Solubility. 5th ed., Tucson, AZ: Univ. Az, College of Pharmacy, **1992.**
Other	Last revision date: 19980602

III. Environmental Fate Endpoints

A. Photodegradation

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	
Method	
Method:	Estimation
Test type:	Atmospheric oxidation
Remarks:	
Results	
Temperature:	25 °C
Hydroxyl radicals reaction	
OH Rate constant:	3.7605 x 1 0^{-12} cm-?/molecule-set
Half-life	2.844 Days (12-hr day; I .5x10^6 OH/cm^3)
Ozone reaction:	**No** ozone reaction estimation
Rc marks:	
Conclusions	Material is oxidized by hydroxyl radicals in the atmosphere at a moderate rate.
Data Quality	
Remarks:	
References	AopWin v I .88; Meylan, W. (1 993). User's Guide for the Estimation Programs Interface (EPI), Version I .2, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

B. **Stability in Water**

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity was >99%
Method	
Method:	OECD- 111 and EEC Annex V, Part C.7.
Test type:	Abiotic Degradation: Hydrolyis as a Function of pH
GLP:	Yes
Remarks:	A preliminary test was performed at 50 °C in which material was dissolved into a pH solution of 4, 7, or 9 at a concentration of 1500 mg/L and % hydrolyzed was determined over time. The rate constants for pH 4 and 7 were derived through Arrhenius relationships in which the logarithm of rate constants at other temperatures (60, 80, and 90 "C) is plotted against the reciprocal of the absolute temperature (K). All studies monitored pH over time.
Results	
Half-life:	pH 4: estimated half life at 2.5 °C is 33 10 hours pH 7: estimated half life at 25 °C is 549 hours pH9: Not determined, greater than 50% hydrolysis occurred in <2.5 hours
Percent hydrolyzed in 5-days (120 hrs) at 50 °C :	pH 4: 17% pH 7: 36% pH 9: 100% (an average of 77 and 8 1% was hydrolyzed after 2.4 hours)
Remarks:	
Conclusions	Material is rapidly hydrolyzed under basic conditions
Data Quality	
Rc marks:	This study followed OECD guidelines and was conducted under GLP assurances.
References	Abiotic Degradation: Hydrolyis as a Function of pH. HAEL Study# 1999-022 1, Eastman Kodak Company, Rochester, NY. June 28, 2000.
Other	

C. Biodegradation

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Unknown
Method	
Method:	Other
Test type:	Hach respirometric and OECD Screening (die-away) tests
GLP:	Unknown
Year:	Unknown
Contact time:	Unknown
Inoculum:	Sewage inoculum from an unknown source
Results	
Degradation % at test end:	Unknown
Classification:	Readily biodegradable
Conclusions	
Data Quality	
Remarks:	Information was extracted from a peer-reviewed publication referenced within the HSDB. However, there was little documentation in regard to methods with only a final conclusion of "Readily Biodegradable" given.
References	Cain RB; Microbial Degradation of Surfactants and "Builder" Components. FEMS Symp 12 (Microb Degr Xenobiotics Recalcitrant Compds) pp 325-70. 1981.
Other	Readers are encouraged to see robust summaries submitted for Ethylene Glycol for more information.

D. Transport between Environmental Compartments (Fugacity)

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	
Method	
Test type:	Estimation
Model used:	Level III Fugacity Model; EPIWIN:EQC from Syracuse Research Corporation
Remarks:	
Results	
Model data and results:	Concentration (%)
Estimated distribution and media concentration (levels IT/III):	Air 1.61 Water 47.7 Soil 50.6 Sediment 0.0595
Remarks:	Physical chemical values utilized in this model were default values obtained from the EPI WIN program.
Conclusions	
Data Quality	
Remarks:	
References	Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 1.2, Syracuse Research Corporation, Syracuse, New York 132 IO. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay *et al.* 1996; *Environ. Toxicol. Chem.* **15(9)**, 16 18- 1626 and 1627- 1 637.
Other	

IV. Ecotoxicity

A. Acute Toxicity to Fish

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity was 99.2%
Method	
Method:	OECD 203 and EEC/Annex V C. 1.
Test type:	Semi-static
GLP:	Yes
Year:	2000
Species/strain:	Fathead minnow *(Pimephales promelas)*
Analytical monitoring:	Yes; Exposure solutions, temperature, pH, dissolved oxygen
Exposure period:	96-Hour
Remarks:	Biological loading was kept below 1 .O g wet weight per liter of test solution, with 14 fish used per exposure level.
Results	
Nominal concentration:	7.5, 15, 30, 60, 120 mg/L
Measured concentration:	6.1, 13.6, 28.5, 57.4, 115.0 mg/L
Endpoint value:	96-hour LC_{50} = 40.45 mg/L, 24-hour LC_{50} = 46.97
Biological observations:	At 24-hours, 100% mortality was observed in the 120 mg/L nominal exposure concentration. At 48-hours, 100% mortality was observed in the 60 mg/L nominal concentration. The minnows in the control, and 7.5, 15, and 30 mg/L nominal concentrations exhibited normal behavior and appearance throughout the test and no significant mortality was observed ($\leq$ 10%).
Statistical methods:	The LC_{50} values were calculated using the SAS statistical software program EC_LC50.SAS (Ver. 1)
Remarks:	The determinations of the LC_{50} values were based on the arithmetic average (for replicates A and B) of the geometric means of the 0 to 48-hour test substance analytical results and the 48 to 96-hour test substance analytical results. The tests were performed in glass chromatography jars containing 20 L of exposure solution, with glass lids scaled with Parafilm®. Exposure temperature ranged from 20-2 1 °C, pH ranged from 7.4 to 8.4, and dissolved oxygen ranged from 6.5 to 9.1 mg/L. Stability determined by analysis of exposure concentrations by GC/FID.
Conclusions	The 96-hour LC_{50} value indicates that the test substance would be classified as "harmful to aquatic organisms" according to the European Union's labeling directive and would correspond to a "moderate concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	An Acute Aquatic Effects Test with the Fathead Minnow *(Pimephales promelas)*; Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY; HAEL No. 1999-022 1; October 6, 2000.
Other	The 96-h LC_{50} value to *P. promelas* following exposure to ethylene glycol was 49,000 mg/L. The basis of this difference is unknown.

B. Acute Toxicity to Aquatic Invertebrates

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity was 99.2%
Method	
Method:	OECD 202 and EEC/Annex V C.2.
Test type:	Acute immobilization, Static
GLP:	Yes
Year:	2000
Species/strain:	Daphnid/*Daphnia magna*
Analytical monitoring:	Yes; Exposure solutions, temperature, pH, dissolved oxygen
Exposure period:	48-Hour
Remarks:	
Results	
Nominal concentration:	120 mg/L
Measured concentration:	116.3 mg/L
Endpoint value:	48-hour EC_{50} >116.3 mg/L
Biological observations:	The daphnids in the dilution water controls and test substance exposure solutions exhibited normal behavior and appearance throughout the test and no significant mortality was observed (≤ 10%) during the study.
Statistical methods:	NA; No significant differences in immobility were noted between treated and control daphnids.
Remarks:	The test substance exposure concentration was based on the arithmetic average (for replicates A and B) of the geometric means of the test substance analytical results at exposure start (time 0) and the test substance analytical results at exposure end (48-hours). Exposure temperature ranged from 20-21 °C, pH ranged from 7.7 to 8.4, and dissolved oxygen ranged from 7.6 to 9.1 mg/L. Stability determined by analysis of exposure concentrations by GC/FID.
Conclusions	The EC_{50} value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	An Acute Aquatic Effects Limit Test with the Daphnid (*Daphnia magna*); Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY; HAEL No. 1999-0221, October 9, 2000
Other	

C. Toxicity to Aquatic Plants

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity was 99.2%
Method	
Method:	OECD 201 and EEC/Annex V C.3.
Test type:	Growth inhibition of algae
GLP:	Yes
Year:	200 1
Species/strain:	*Selenastrum capricornutum*
Endpoint basis:	Cell concentrations (biomass) and growth rate
Exposure period:	72-hours
Analytical procedures:	Temperature, light intensity, rpm, and test substance concentration were assessed at the 0, 24, 48, and 72 hours. The pH was assessed at time 0 and after 72 hours.
Remarks:	
Results	
Nominal concentration:	125.0 mg/L
Measured concentration:	1 19.86 mg/L (geometric mean over all time points)
Endpoint value:	E_bC_{50} and E_rC_{50} > 119.86 mg/L; The 72-hour NOEC was determined to be 119.86 mg/L (highest concentration tested).
Biological observations:	None
Was control response satisfactory:	Yes (control culture concentrations increased by a factor of 72-fold)
Statistical methods:	NOEC value was determined through use of SAS statistical software program AL-ACUTE (Ver. 2.2). The E_bC_{50} and E_rC_{50} were inestimable as greater than 50% inhibition in growth and/or biomass was not achieved in this limit test.
Remarks:	A mean illumination of 754 foot-candles was maintained. The mean temperature was 24°C and pH ranged from 7.4 to 7.6. Cultures were oscillated at 100 rpm. Stability determined by analysis of test substance in the test media by GC/FID. No protocol deviations were noted.
Conclusions	The 72-hour E_bC_{50} and E_rC_{50} values indicate that, based on this study, the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under CLP assurances.
References	A Growth Inhibition Limit Test with the Alga, *Selenastrum capricornutum*; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-5 12-900134-A; January 30, 2001.
Other	

V. Toxicological Data

A. Acute Toxicity

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity was unknown
Method	
Method:	Acute lethality; Other
Test type:	LD_{50} estimate
GLP:	No (Pre-GLP)
Year:	1941
Species/strain:	Rat/Wistar
Sex:	Male
Animals/sex/dose:	1 O/dose
Vehicle:	Water
Route of exposure:	Oral gavage
Remarks:	It was noted that there were IO animals per dose.
Results	
Value:	LD_{50} = 6.86 g/kg.
Deaths at each dose:	Unknown
Remarks:	
Conclusions	Material would be considered as practically nontoxic.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	The study was conducted quite some time ago and hence many study details are missing, however basic data are given and results indicate the material is not acutely toxic.
References	Smyth, H.F., Seaton, J., and Fischer, L. (1941). The Single Dose Toxicity of Some Glycols and Derivatives. *J. Id. Hyg. Toxicol.* **23(6):** *259-268.*
Other	

B. Repeated Dose Toxicity

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity was unknown
Method	
Method:	Other
Test type:	Repeated exposure
GLP:	No
Year:	1943
Species/strain:	Rat
Route of exposure:	Drinking water
Duration of test:	Up to 131 days
Dose levels:	1, 3, and 5 %
Sex:	Both
Exposure period:	10 Females received 5% solutions for up to 37 days while 5 males were exposed to a 1% solution for 110 days, then on Day I I I given a 3% drinking water solution for another 20 days.
Post-exposure observation period:	None
Remarks:	
Results	
NOAEL (NOEL):	1%
Actual doses received:	Unknown
Toxic responses by dose:	Rats receiving the 5% solution soon became ill and ate less. One rat died after a week while the last animal was terminated in a moribound state on Day 37. The kidneys of the rat that died after one week were tilled with calcium oxalate crystals and were indistinguishable from other test animals that had received ethylene glycol. Animals exposed to a 1% solution grew and appeared normal out to Day I IO. Of the animals consuming a 3% test solution for 20 more days, three had markedly enlarged kidneys. The surface was mottled with masses of crystals that extended deep into the cortex.
Statistical methods:	Unknown
Remarks:	
Conclusions	It appears that exposure to the diacetate ester of ethylene glycol leads to the formation of calcium oxalate urinary crystals in a manner similar to that of ethylene glycol alone. This strongly suggests the two acetate moieties are cleaved off from the parent glycol.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	While the study report lacked a significant amount of information and overall robustness, it nevertheless still indicates that exposure to the diacetate compound induces renal effects similar to that of ethyleneglycol.
References	Mulinos, M.G., Pomerantz, L., and Lojkin, M. E. (1943). The Metabolism and Toxicology of Ethylene Glycol and Ethylene Glycol Diacetate. *Amer. Jour. Pharm.*, **115: 51-63.**
Other	Please see an assessment of this end point in the Ethylene Glycols category of chemicals under the International Council of Chemical Associations (ICCA) High Production Volume (HPV) Initiative.

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity was unknown
Method	
Method:	Other
Test type:	Repeated exposure
GLP:	No
Year:	1939
Species/strain:	Rat
Route of exposure:	Oral
Duration of test:	7 - 130 days
Dose levels:	1 - 5 %
Sex:	Unknown
Exposure period:	Daily in drinking water
Post-exposure observation period:	None
Remarks:	Eleven animals total were used. The report does not indicate exactly how many animals received each dose level.
Results	
LOAEL:	The minimal dose required to produce damage in the kidneys was approximately 6 g/kg received in a 5% concentration for 7 days.
Actual doses received:	Unknown
Toxic responses by dose:	It was noted that 4 animals died between 7 and 114 days, all were noted as having lesions present in the kidneys. Kidneys from 4 of the remaining 7 animals also had lesions. These animals were killed at intervals between Day 15 and 130. Lesions were due to the presence of calcium oxalatc crystals. There were no histopathological abnormalities noted in the parathyroid glands.
Statistical Methods:	None were noted
Remarks:	
Conclusions	It appears that exposure to the diacetate ester of ethylene glycol leads to the formation of calcium oxalate urinary crystals in a manner similar to that of ethylene glycol alone. This strongly suggests the two acetate moieties arc cleaved off from the parent glycol.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	While the study report lacked a significant amount of information and overall robustness, its primary value lies in its utility showing that an exposure to ethylene glycol diacetate induces renal effects similar to that seen following exposure to ethylene glycol alone.
References	Kesten, H.D., Mulinos, M.G., and Pomerantz, L. (I 939). Pathologic Effects of Certain Glycols and Related Compounds. *Arch. Path.*, 27:447-465.
Other	Please see an assessment of this end point in the Ethylene Glycols category of chemicals under the International Council of Chemical Associations (ICCA) High Production Volume (HPV) Initiative.

C. Genetic Toxicity - Mutation

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity was >99%
Method	
Method:	EEC Annex V Guideline number B. 14, "Other Effects-Mutagenicity *Salmonella typhimurium*-Reverse Mutation Assay", and Guideline number B. 13, Other Effects-Mutagenicity, *Escherichia* c&-Reverse Mutation Assay"
Test type:	*In vitro* mutagenicity
GLP:	Yes
Y car:	2000
Species/strain:	*Salmonella typhimurium*/TA98, 100, 1535, 1537, and *Escherichia coli*/WP2*uvr*A(pKM 10 1)
Metabolic activation:	Yes; Aroclor 1254-induced SD rat liver S9
Concentration tested:	Maximum concentration tested was 5000 ug/plate
Remarks:	Positive controls (2-aminoanthracene, 2-nitrofluorene, sodium azide, ICR-19 1, and 4-nitroquinoline-N-oxide) were run concurrently. Water was used as a vehicle and vehicle control.
Results	
Result:	No positive responses were induced in any of the tester strains
Cytotoxic concentration:	>5000 ug/plate (no evidence of cytotoxicity was seen)
Precipitation concentration:	No precipitate was noted in the report.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	A mean and standard deviation are calculated on the number of revertants.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented EEC Annex guideline study conducted under GLP assurances at Covance Laboratories Inc., Vienna, VA.
References	Covance study number: 21034-0-409R; February 8, 2000
Other	

D. Genetic Toxicity – Chromosomal Aberrations

Test Substance	
Test substance:	Ethylene Glycol Diacetate
Remarks:	Purity was >99%
Method	
Method:	OECD: TG-473
Test type:	*In vitro* mammalian chromosomal aberrations assay
GLP:	Yes
Year:	2000
Species/strain:	Chinese hamster ovary cells (CHO)
Concentrations tested:	10.2 - 1500 ug/ml (this level meets the 10 mM max. recommended level)
Metabolic Activation:	Yes; Aroclor 1254-induced SD rat liver S9
Remarks:	The positive controls consisted of mitomycin-C and cyclophosphamide. Negative control was the test vehicle water.
Results	
Result:	No significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed in the analyzed cultures at any concentration.
Cytotoxic concentration:	> 1500 ug/ml (no signs of toxicity were noted)
Precipitation concentration:	No precipitate was observed at the maximum concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Statistical analysis employed a Cochran-Armitage test for linear trends and Fisher's Exact Test to compare the percentage of cells with aberrations.
Remarks:	
Conclusions	Material was not genotoxic (did not induce any structural or numerical aberrations) under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Covance Laboratories Inc., Vienna, VA; Study number: 21034-0-437OECD; March 21, 2000.
Other	

E. Developmental Toxicity

Please see an assessment of this end point in the Ethylene Glycols category of chemicals under the International Council of Chemical Associations (ICCA) High Production Volume (HPV) Initiative.

F. Toxicity to Reproduction

Please see an assessment of this end point in the Ethylene Glycols category of chemicals under the International Council of Chemical Associations (ICCA) High Production Volume (HPV) Initiative.